REMARKS

Claims 170-172, 174-178, and 188-197 were pending, and of these Claims 175-178, 189, 191, 193-195 and 197 were withdrawn. By virtue of the instant response, Claims 170, 176, and 190 were amended, and Claims 174, 175, and 194 were canceled. As such Claims 170-172, 176-178, 188-193 and 195-197 are currently pending.

I. Priority

As requested. Applicants hereby update the status of the parent US applications identified in the priority statement on page 1 of the Specification to indicate that they have been issued as US Patent Nos. 7,320,795 (from application 10/630,070), and 7,144,712 (from application 10/630,074), respectively.

II. Information Disclosure Statement

Applicants thank the Examiner for consideration of the Information Disclosure Statement (IDS) submitted on October 18, 2007.

III. Claim Rejections - 35 U.S.C. § 102

A. Claims 170-172 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by Paoletti et al., Vaccine 20:370-76, of record in the IDS ("Paoletti").

The Examiner states that "Paoletti teaches a method for inducing an immune response to a target antigen comprising the administration of a duck hepatitis B (a hepadnavirus) core antigen coupled with a heterologous antigen (a streptococcal antigen)" (Office Action, page 4). Applicants respectfully traverse this rejection and its supporting remarks. Even so, Applicants hereby amend Claims 170, 176 and 190, and canceled Claims 174, 175 and 194, in order to further the prosecution of the present application and Applicants' business interests, without acquiescing to the Examiner's arguments, while reserving the right to prosecute the original, similar or broader claims in one or more future application(s). Specifically, Applicants hereby amend Claim 170 to recite "a hybrid particle comprising a fusion protein comprising a rodent hepadnavirus core antigen and a

heterologous antigen," and withdrawn Claim 176 to recite "a hybrid particle comprising a fusion protein comprising a non-human primate hepadnavirus core antigen and a heterologous antigen." Support for this amendment can be found but is not limited to Claim 174, now canceled, and the definition of the term "hybrid," which when "used in reference to a hepadna virus core antigen, refers to a fusion protein of the hepadna virus core antigen and an unrelated antigen" (US 2008/0131452, paragraph [0153]). Thus no new matter has been introduced.

Paoletti discloses the production of recombinant *duck* hepatitis B core antigen *covalently coupled to purified streptococcal capsular polysaccharide* (Paoletti, abstract). In contrast, the amended claims are directed to a fusion protein comprising a heterologous polypeptide antigen, which in the embodiments of Claim 170-172 comprises a rodent hepadnavirus core antigen. Since the methods of Paoletti are directed to administration of a glycoconjugate of an avian hepadnavirus core antigen, whereas Claims 170-172 as amended are directed to administration of a fusion protein comprising a rodent hepadnavirus core antigen, Paoletti does not anticipate Claims 170-172. As such, withdrawal of this rejection is respectfully requested.

B. Claims 170-172, 174, 190, 192, and 196 stand rejected under 35 U.S.C. 102(a) as allegedly anticipated by Birkett et al., US 2003/0054337, of record in the IDS ("Birkett").

The Examiner states that "Birkett teaches HBc particles for delivery of a heterologous epitope...[and the] reference indicates that the HBc particles may be derived from the core particles of HBV, or of other related hepadnaviruses such as the core antigen of the ground squirrel hepatitis virus" (Office Action, page 4). Applicants respectfully traverse this rejection and its supporting remarks. Even so as described above, Claim 170 has been amended to recite "a rodent hepadnavirus core antigen."

Section 2121.01 of the MPEP states that "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." The actual and prophetic examples of Birkett are restricted to the disclosure of

human hepatitis B virus core antigen (HBcAg) comprising heterologous amino acids peptide-bonded to a only a limited number of positions within HBcAg. Absent Applicants' disclosure undue experimentation was required to produce the particles required by the claims. Applicants believe they were the first to successfully prepare ground squirrel and woodchuck hepatitis virus cores that assemble as hybrid particles.

Section 2121.02 of the MPEP instructs that "[w]here a process for making the compound is not developed until after the date of invention, the mere naming of a compound in a reference, without more, cannot constitute a description of the compound." Applicants contend that prior to development of the combinatorial technology provided in the present lineage, a significant proportion of hybrid HBcAg (as well as WHcAg) cores could not be produced due to well-known problems in particle assembly (See. e.g., Jegerlehner et al., Vaccine, 20:3104-3112, 2002 and Karpenko et al., Amino Acids, 18:329-337,2000). Furthermore, not all hybrid HBcAg and WHcAg cores can be expressed, let alone assemble to properly present a heterologous antigen to an antibody. Birkett clearly illustrates this point in the section of Example 4 devoted to expression failures, and Table 7, which provides a listing of numerous "epitopes that have failed to express when inserted between D78 and P79 (V2) in a HBc chimer" (Birkett, paragraph [0266]. Similarly, Applicants have found that a truncated WHcAg having a Cys^{151} at the carboxy-terminus did not assemble as hybrid particles when recombinantly expressed from multiple constructs: M epitope insert at position 74, CE epitope insert at position 74, HV-2 epitope insert at position 75, HV-3 epitope insert at position 74. HV-3 epitope insert at position 75, HV-4 epitope at position 74, CD40L immune enhancer insert at the carboxy-terminus, and IM2(·) insert at position 78 (Specification, Table 13). However, these epitopes were successfully expressed and assembled as hybrid WHcAg particles when alternative C-termini were used. Altering the insert position and/or C-terminus to rescue hybrid particle assembly is one example of the utility of the combinatorial technology of Applicants' disclosure. Birkett does not provide this critical teaching.

As Birkett does not produce hybrid particles comprising a rodent hepadnavirus core as recited in the amended claims, and does not provide the teaching required for their production,

Birkett is not an anticipatory reference. As such, withdrawal of this rejection is respectfully requested.

IV. Claim Rejections - 35 USC § 103

A. Claim 188 stands rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Paoletti.

The Examiner states that Paoletti "does not actually disclose the administration of the conjugate to a human as described by claim 188[, h]owever, the reference teaches that the duck hepadnaviral core protein does not react with antibodies directed to human HBV" (Office Action, page 5). Applicants respectfully traverse this rejection and its supporting remarks. However, as discussed above in Section III, Claims 170 and 176 have been amended to recite a "fusion protein." In addition Claim 170 has been amended to recite a "rodent hepadnavirus core antigen."

Since Paoletti discloses production of a *glycoconjugate comprising an avian hepadnavirus core antigen*, and not a fusion protein comprising a rodent hepadnavirus core antigen as recited in the amended claims, Paoletti does not render the pending claims obvious. As such, withdrawal of this rejection is respectfully requested.

B. Claims 170-172, 174, 188, 190, 192, and 196 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Birkett in view Paoletti, Maruyama et al., Gastroenterol 106:1006-15 ("Maruyama"), and Shödel et al., Vaccine 11:624-28 of record in the IDS (Shödel).

In making this rejection, the Examiner relies upon Paoletti for the suggestion to use duck hepatitis core antigen as a carrier for delivery of antigens to humans due to the lack of cross-reactivity between antibodies to the core antigens of the human and duck hepatitis B viruses. Similarly, the disclosures of Maruyama and Shödel were relied upon for teachings of a low level of cross-reactivity of antibodies between the core antigens of human and rodent hepadnavirus. Birkett on the other hand, was relied upon for the suggestion to substitute human core antigens with core antigens of hepadnaviruses of other species (Office Action, page 6).

Applicants respectfully traverse this rejection and its supporting remarks. The teachings cited by the Examiner do not bring an ordinary person skilled in the art in possession of the claimed methods. In the first place, the amended claims require "a hybrid particle comprising a fusion protein comprising a rodent hepadnavirus core antigen and a heterologous antigen." In contrast, of the four references cited by the Examiner, Birkett is the only reference that actually teaches the production of a fusion protein, albeit a fusion protein comprising a *human hepatitis virus core antigen (HBcAg)*. However, the preparation of hybrid particles comprising a rodent hepadnavirus core antigen is not obvious based upon the teaching of hybrid particles comprising HBcAg, because the structure of HBcAg is significantly different than that of the rodent cores. Section 2144.08 of the MPEP instructs the Examiner to consider "any teaching or suggestion in the reference of a preferred species or subgenus that is significantly different in structure from the claimed species or subgenus[, as s]uch a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness." To this end Birkett simply states "[l]ess preferred still are the sequences of woodchuck and ground squirrel at aligned positions 2·through 149" (Birkett, paragraph [0118]). Importantly, the ground squirrel hepatitis virus core antigen (GSHcAg) and woodchuck hepatitis virus core antigen (WHcAg) are each only 67% identical at the amino acid level to the human hepatitis B virus core antigen (HBcAg) preferred by Birkett (US 2008/0131452, paragraphs [208] and [215]).

On the other hand, the structural similarity of the GSHcAg and the WHcAg is much greater than the structural similarity between the rodent and human cores. Specifically, the amino acid sequence identity of the GSHcAg and the WHcAg is 91% (US 2008/0131452, paragraph [214]), and this high degree of homology is reflected in the similarity of the humoral and cellular immune responses elicited by these cores antigens. In particular, a high level of cross reactivity was observed between the GSHcAg and WHcAg at both the antibody level (Specification, Fig. 6 and Table 19) and at the $CD4^+$ level (Specification, Fig. 43 and Table 20) during development of the present invention. Thus Applicants contend that it is improper to extrapolate from Birkett's teaching regarding the expression, assembly and antigenicity of hybrid HBcAg cores to that of hybrid rodent cores, because of significant structural differences. In contrast, it is reasonable to

extrapolate from Applicants' teaching regarding the expression, assembly and antigenicity of hybrid WHcAg cores to that of hybrid ground squirrel, and other rodent cores because of significant structural similarities.

As additional evidence of the non-obviousness of the claimed methods, Applicants hereby submit a copy of a Declaration signed by Darrell Peterson ("Peterson Declaration" attached hereto at Tab A), a co-author of the cited Paoletti and Maruyama references. Although the Peterson Declaration was originally drafted in support of a parent application, it is informative as to the patentability of the pending claims because Section 4 addresses why one of skill in the art would not have been motivated to substitute an exemplary rodent hepadnavirus core (WHcAg) for the HBcAg of Birkett for producing an epitope carrier.

Based on the minimal structural similarity between the hybrid particles of the cited art and the hybrid particles of the amended claims, the lack of teaching provided by the cited art regarding their production, and the rebuttal evidence provided herewith, withdrawal of this rejection is respectfully requested.

V. Double Patenting

A. Claims 170-172 and 174 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 1-11 and 14-28 of U.S. Patent No. 7,320,795. In addition, Claim 188 stands rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 1-11 and 14-28 of U.S. Patent No. 7,320,795 in view of the teachings of Paoletti, Maruyama, and Shödel. Applicants respectfully disagree with these rejections. However, in the interest of advancing prosecution in this case, enclosed herewith is a terminal disclaimer over the '795 Patent.

B. Claims 170-172, 174, 192 and 196 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 32, 36-44, 47-64 of co-pending Application No. 12/008,059. In addition, Claim 188 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over

Claims 32, 36-44, 47-64 of co-pending Application No. 12/008,059, further in view of Paoletti, Maruyama, and Shödel. Applicants respectfully disagree with this rejection. However, in the interest of advancing prosecution in this case, enclosed herewith is a terminal disclaimer over the '059 Application.

VI. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **643802000203**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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